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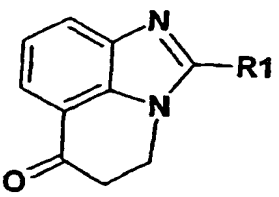
(54) Title: KNOWN AND NOVEL 4,5-DIHYDRO-IMIDAZO[4,5,1-IJ]QUINOLIN-6-ONES USEFUL AS POLY(ADP-RIBOSE)POLYMERASE INHIBITORS



(1)

(57) Abstract: Compounds of the formula (1), in which R1 has the meanings indicated in the description, are novel active poly(ADP-ribosyl)transferase (PARP) inhibitors.

KNOWN AND NOVEL 4,5-DIHYDRO-IMIDAZO(4,5,1-IJ)QUINOLIN-6-ONES USEFUL AS POLY(ADP -RIBOSE) POLYMERASE INHIBITORS

Field of application of the invention

The invention relates to known and novel 4,5-Dihydro-imidazo[4,5,1-ij]quinolin-6-ones, which are used in the pharmaceutical industry for the production of pharmaceutical compositions.

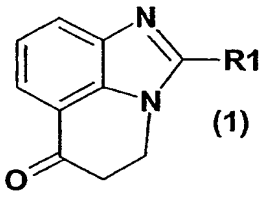
Known technical background

In the International patent applications WO00/42040, WO01/23386 and WO01/23390 3,4-Dihydro-1,2a,4-triaza-acenaphthylen-5-one derivatives are described as poly(ADP-ribosyl)transferase (PARP) inhibitors. In the European patent application EP 0405442 4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one derivatives are described with hypotensive, anti-oedematous and diuretic effects. In the European patent application EP 0646583 4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one derivatives are described as inhibitors for types 5-HT_3 and 5-HT_4 serotoninergic receptors. In the International patent application WO02/12239 4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one derivatives which are substituted by piperazinyl- or piperidinyl groups are disclosed as poly(ADP-ribosyl)transferase (PARP) inhibitors.

Description of the invention

It has now been found that the known and novel 4,5-Dihydro-imidazo[4,5,1-ij]quinolin-6-ones described in greater detail below have surprising and particularly advantageous properties.

In a first aspect the invention relates to compounds of the formula 1,



(1)

in which

R1 is aryl1, aryl1 substituted by R2, R3 and R4, 3-7C-cycloalkyl, 3-7C-cycloalkyl substituted by R2, R3 and R4, or aryl4,

R2 is halogen, hydroxyl, cyano, nitro, hydroxycarbonyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy completely or predominantly substituted by fluorine, 1-4C-alkylthio, 1-4C-alkylsul-

fonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino, mono- or di-1-4C-alkylaminocarbonyl, mono-or di-1-4C-alkylaminosulfonyl, phenoxy, benzyloxy or aryl3,

R3 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino or mono- or di-1-4C-alkylaminocarbonyl,

R4 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

aryl1 is phenyl, furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl or triazinyl,

aryl2 is phenyl, furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl or triazinyl,

aryl3 is aryl2, aryl2 substituted by R5, R6 and R7, aryl4 or aryl4 substituted by R5, R6 and R7,

aryl4 is a condensed bicyclic ring system - of which at least one ring is aromatic - containing 8 to 10 carbon atoms, which optionally can be replaced by up to four heteroatoms selected from the group consisting of O, N and S,

R5 is halogen, hydroxyl, cyano, nitro, hydroxycarbonyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy completely or predominantly substituted by fluorine, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino, mono- or di-1-4C-alkylaminocarbonyl, mono-or di-1-4C-alkylaminosulfonyl or phenyl,

R6 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino or mono- or di-1-4C-alkylaminocarbonyl,

R7 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

and the salts, the N-oxides and the salts of the N-oxides of these compounds for use in the treatment of diseases.

In a second aspect the invention relates to use of compounds of formula 1 in which

R1 is aryl1, aryl1 substituted by R2, R3 and R4, 3-7C-cycloalkyl, 3-7C-cycloalkyl substituted by R2, R3 and R4, or aryl4,

R2 is halogen, hydroxyl, cyano, nitro, hydroxycarbonyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy completely or predominantly substituted by fluorine, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino, mono- or di-1-4C-alkylaminocarbonyl, mono-or di-1-4C-alkylaminosulfonyl, phenoxy, benzyloxy or aryl3,

R3 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino or mono- or di-1-4C-alkylaminocarbonyl,

R4 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

aryl1 is phenyl, furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl or triazinyl,

aryl2 is phenyl, furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl or triazinyl,

aryl3 is aryl2, aryl2 substituted by R5, R6 and R7, aryl4 or aryl4 substituted by R5, R6 and R7,

aryl4 is a condensed bicyclic ring system - of which at least one ring is aromatic - containing 8 to 10 carbon atoms, which optionally can be replaced by up to four heteroatoms selected from the group consisting of O, N and S,

R5 is halogen, hydroxyl, cyano, nitro, hydroxycarbonyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy completely or predominantly substituted by fluorine, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino, mono- or di-1-4C-alkylaminocarbonyl, mono-or di-1-4C-alkylaminosulfonyl or phenyl,

R6 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino or mono- or di-1-4C-alkylaminocarbonyl,

R7 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

and the salts, the N-oxides and the salts of the N-oxides of these compounds for the preparation of pharmaceutical compositions for the treatment of diseases which can be ameliorated by the administration of PARP inhibitors.

1-4C-Alkyl represents a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Examples which may be mentioned are the butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl and preferably the ethyl and methyl radicals.

1-4C-Alkoxy represents radicals which, in addition to the oxygen atom, contain a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Examples which may be mentioned are the butoxy, isobutoxy, sec-butoxy, tert-butoxy, propoxy, isopropoxy and preferably the ethoxy and methoxy radicals.

Halogen within the meaning of the invention is bromine, chlorine or fluorine.

3-7C-Cycloalkyl represents cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, of which cyclopropyl, cyclobutyl and cyclopentyl are preferred.

1-4C-Alkylthio radicals contain, in addition to the sulfur atom, one of the abovementioned 1-4C-alkyl radicals. Examples are the methylthio and the ethylthio radical.

1-4C-Alkylsulfonyl is a sulfonyl group to which one of the abovementioned 1-4C-alkyl radicals is bonded. An example is the methanesulfonyl radical [CH_3SO_2-].

1-4C-Alkoxycarbonyl represents a carbonyl group to which one of the abovementioned 1-4C-alkoxy radicals is bonded. Examples which may be mentioned are the methoxycarbonyl [CH_3O-C(O)-] and the ethoxycarbonyl [CH_3CH_2O-C(O)-] radicals.

An 1-4C-Alkylcarbonylamino radical is, for example, the propionylamino [$C_3H_7C(O)NH$-] and the acetylamino radical [$CH_3C(O)NH$-].

1-4C-Alkoxy which is completely or predominantly substituted by fluorine is, for example, the 2,2,3,3,3-pentafluoropropoxy, the perfluoroethoxy, the 1,2,2-trifluoroethoxy and in particular the 1,1,2,2-tetrafluoroethoxy, the 2,2,2-trifluoroethoxy, the trifluoromethoxy and the difluoromethoxy radical, of which the difluoromethoxy radical is preferred. "Predominantly" in this connection means that more than half of the hydrogen atoms of the 1-4C-alkoxy radical are replaced by fluorine atoms.

Mono- or Di-1-4C-alkylamino radicals contain in addition to the nitrogen atom, one or two of the abovementioned 1-4C-alkyl radicals. Preferred are the di-1-4C-alkylamino radicals, especially the dimethylamino, the diethylamino and the diisopropylamino radical.

Mono- or Di-1-4C-alkylaminocarbonyl radicals contain in addition to the carbonyl group one of the abovementioned mono- or di-1-4C-alkylamino radicals. Examples which may be mentioned are the N-methyl- the N,N-dimethyl-, the N-ethyl-, the N-propyl-, the N,N-diethyl- and the N-isopropylaminocarbonyl radical.

Mono-or Di-1-4C-alkylaminosulfonyl stands for a sulfonyl group to which one of the abovementioned mono- or di-1-4C-alkylamino radicals is bonded. Examples which may be mentioned are the methylaminosulfonyl, the dimethylaminosulfonyl and the ethylaminosulfonyl radical.

In case aryl1 represents a phenyl group, the substitutents R2, R3 and R4 can be in ortho, meta and para position relative to the bond between the phenyl group and the 4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one group; the meta and para position(s) are preferred in this connection.

The group aryl4 is a condensed bicyclic ring system - of which at least one ring is aromatic - containing 8 to 10 carbon atoms, which optionally can be replaced by up to four heteroatoms selected from the group consisting of O, N and S. Examples of aryl4 groups which may be mentioned are naphthalinyl, quinolinyl, isoquinolinyl, chinazolinyl, chinoxalinyl, cinnolinyl, phthalazinyl, naphthyridinyl, indolizinyl, indolyl, indazolyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, benzofuranyl, benzothiophenyl, pteridinyl, purinyl, indolinyl, isoindolinyl, indanyl, 1,2,3,4-tetrahydronaphthalenyl and benzo[1,3]dioxolyl.

Possible salts for compounds of the formula 1 - depending on substitution - are all acid addition salts or all salts with bases. Particular mention may be made of the pharmacologically tolerable salts of the inorganic and organic acids and bases customarily used in pharmacy. Those suitable are, on the one

hand, water-soluble and water-insoluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulfuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)benzoic acid, butyric acid, sulfosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulfonic acid, methanesulfonic acid or 3-hydroxy-2-naphthoic acid, it being possible to employ the acids in salt preparation - depending on whether a mono- or polybasic acid is concerned and depending on which salt is desired - in an equimolar quantitative ratio or one differing therefrom.

On the other hand, salts with bases are also suitable. Examples of salts with bases which may be mentioned are alkali metal (lithium, sodium, potassium) or calcium, aluminium, magnesium, titanium, ammonium, meglumine or guanidinium salts, where here too the bases are employed in salt preparation in an equimolar quantitative ratio or one differing therefrom.

Pharmacologically intolerable salts which can initially be obtained, for example, as process products in the preparation of the compounds according to the invention on an industrial scale are converted into pharmacologically tolerable salts by processes known to the person skilled in the art.

It is known to the person skilled in the art that the compounds according to the invention and their salts, when they are isolated, for example, in crystalline form, can contain various amounts of solvents. The invention therefore also comprises all solvates and in particular all hydrates of the compounds of the formula 1, and also all solvates and in particular all hydrates of the salts of the compounds of the formula 1.

In a further aspect the invention relates to new compounds of formula 1.

One embodiment (embodiment A) of the compounds of formula 1 are those compounds
in which

R1 is phenyl substituted by R2, R3 and R4,

wherein either

R2 is 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkylcarbonylamino, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, mono-or di-1-4C-alkylaminosulfonyl, benzyloxy or aryl3,

R3 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino or mono- or di-1-4C-alkylaminocarbonyl and

R4 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

or

R2 is halogen, hydroxyl, cyano, nitro, hydroxycarbonyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy completely or predominantly substituted by fluorine, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonylamino, amino, aminocar-

bonyl, mono- or di-1-4C-alkylamino, mono- or di-1-4C-alkylaminocarbonyl, mono-or di-1-4C-alkylaminosulfonyl, phenoxy, benzyloxy or aryl3,

R3 is 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkylcarbonylamino, aminocarbonyl or mono- or di-1-4C-alkylaminocarbonyl and

R4 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

aryl2 is phenyl, furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl or triazinyl,

aryl3 is aryl2, aryl2 substituted by R5, R6 and R7, aryl4 or aryl4 substituted by R5, R6 and R7,

aryl4 is a condensed bicyclic ring system - of which at least one ring is aromatic - containing 8 to 10 carbon atoms, which optionally can be replaced by up to four heteroatoms selected from the group consisting of O, N and S,

R5 is halogen, hydroxyl, cyano, nitro, hydroxycarbonyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy completely or predominantly substituted by fluorine, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino, mono- or di-1-4C-alkylaminocarbonyl, mono-or di-1-4C-alkylaminosulfonyl or phenyl,

R6 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino or mono- or di-1-4C-alkylaminocarbonyl,

R7 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

Compounds of embodiment A to be emphasized are those in which

R1 is phenyl substituted by R2, R3 and R4,

wherein either

R2 is 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkylcarbonylamino or benzyloxy,

R3 is hydrogen, halogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino or mono- or di-1-4C-alkylaminocarbonyl and

R4 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

or

R2 is hydroxyl, cyano, nitro, hydroxycarbonyl, trifluoromethyl, 1-4C-alkoxy completely or predominantly substituted by fluorine, 1-4C-alkylcarbonyl or benzyloxy,

R3 is 1-4C-alkylthio, 1-4C-alkylsulfonyl or 1-4C-alkylcarbonylamino and

R4 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

Further compounds of embodiment A to be emphasized are those in which

R1 is phenyl substituted by R2, R3 and R4,

wherein

R2 is aryl3,

R3 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino or mono- or di-1-4C-alkylaminocarbonyl and

R4 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

aryl2 is phenyl, furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl or triazinyl,

aryl3 is aryl2, aryl2 substituted by R5, R6 and R7, aryl4 or aryl4 substituted by R5, R6 and R7,

aryl4 is a condensed bicyclic ring system - of which at least one ring is aromatic - containing 8 to 10 carbon atoms, which optionally can be replaced by up to four heteroatoms selected from the group consisting of O, N and S,

R5 is halogen, hydroxyl, cyano, nitro, hydroxycarbonyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy completely or predominantly substituted by fluorine, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino, mono- or di-1-4C-alkylaminocarbonyl, mono-or di-1-4C-alkylaminosulfonyl or phenyl,

R6 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino or mono- or di-1-4C-alkylaminocarbonyl,

R7 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

Preferred compounds of embodiment A are those in which

R1 is phenyl substituted by R2, R3 and R4,

wherein either

R2 is 1-4C-alkylthio, 1-4C-alkylsulfonyl or 1-4C-alkylcarbonylamino,

R3 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy and

R4 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

or

R2 is benzyloxy,

R3 is hydrogen and

R4 is 1-4C-alkoxy,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

Further preferred compounds of embodiment A are those in which

R1 is phenyl substituted by R2, R3 and R4,

wherein either

R2 is 1-4C-alkylsulfonyl or 1-4C-alkylcarbonylamino,

R3 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy and

R4 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

or

R2 is benzyloxy,

R3 is hydrogen and

R4 is 1-4C-alkoxy,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

Still further preferred compounds of embodiment A are those in which

R1 is phenyl substituted by R2, R3 and R4,

wherein

R2 is aryl 4, aryl2 or aryl2 substituted by R5, R6 and R7,

R3 is hydrogen, 1-4C-alkyl or 1-4C-alkoxy,

R4 is hydrogen, 1-4C-alkyl or 1-4C-alkoxy,

aryl2 is phenyl, furanyl, thiophenyl, pyrrolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl,

aryl4 is quinolinyl, benzo[1,3]dioxolyl, indolyl or naphthalenyl,

R5 is halogen, hydroxyl, cyano, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonylamino, di-1-4C-alkylamino or amino,

R6 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

R7 is hydrogen or 1-4C-alkoxy,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

Particularly preferred compounds of embodiment A are those in which

R1 is phenyl substituted by R2, R3 and R4,

wherein either

R2 is methylthio, methylsulfonyl or methylcarbonylamino,

R3 is hydrogen and

R4 is hydrogen,

or

R2 is benzyloxy,

R3 is hyrogen and

R4 is methoxy,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

Further particularly preferred compounds of embodiment A are those in which

R1 is phenyl substituted by R2, R3 and R4,

wherein either

R2 is methylsulfonyl or methylcarbonylamino,

R3 is hydrogen and

R4 is hydrogen,

or

R2 is benzyloxy,

R3 is hydrogen and

R4 is methoxy,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

Still further particularly preferred compounds of embodiment A are those in which

R1 is phenyl substituted by R2, R3 and R4,

wherein either

R2 is aryl4, aryl2 or aryl2 substituted by R5, R6 and R7,

R3 is hydrogen,

R4 is hydrogen,

aryl2 is phenyl, furanyl, thiophenyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl or pyrimidinyl,

aryl4 is quinolinyl, benzo[1,3]dioxolyl, indolyl or naphthalenyl,

R5 is halogen, hydroxyl, cyano, 1-4C-alkyl, trifluoromethyl, methoxy, methoxycarbonyl, acetyl, methylcarbonylamino, dimethylamino or amino,

R6 is hydrogen, 1-4C-alkyl or 1-4C-alkoxy,

R7 is hydrogen or 1-4C-alkoxy,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

Selected compounds of embodiment A are those in which

R1 is 4-methylsulfanylphenyl, 4-acetylaminophenyl, 3-benzyloxy-4-methoxyphenyl or 4-methansulfonylphenyl,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

Further selected compounds of embodiment A are those in which

R1 is biphenyl-4-yl, 4-pyridin-2-ylphenyl, 4-pyridin-4-ylphenyl, 4-pyridin-3-ylphenyl, 4-(3,5-dimethyl-isoxazol-4-yl)phenyl, 4-thiophen-2-ylphenyl, 4-thiophen-3-ylphenyl, 4'-fluorobiphenyl-4-yl, 3'-fluorobiphenyl-4-yl, 4-benzo[1,3]dioxol-5-ylphenyl, 4-furan-3-ylphenyl, 4-pyridin-2-ylphenyl, 3'-carbonitril-biphenyl-4-yl, 4'-methoxy-biphenyl-4-yl, 3'-amino-biphenyl-4-yl, 4-(2,4-dimethoxy-pyrimidin-5-yl)phenyl, 3'-acetyl-biphenyl-4-yl, 4-quinolin-3-ylphenyl, 4'-trifluoromethyl-biphenyl-4-yl, 4-(2-methoxypyridin-3-yl)phenyl, 3',4'-dimethoxy-biphenyl-4-yl, 3'-methoxycarbonyl-biphenyl-4-yl, 3-furan-3-ylphenyl, 4'-methoxycarbonyl-biphenyl-4-yl, 4-(1H-indol-6-yl)phenyl, 3'-trifluoromethyl-biphenyl-4-yl, 3-thiophen-3-ylphenyl, 3'-acetamide-biphenyl-4-yl, 3'-amino-biphenyl-3-yl, 3-furan-2-ylphenyl, 3'-methoxy-biphenyl-4-yl, 3-pyridin-4-ylphenyl, 3'-carbonitril-biphenyl-3-yl, 3-(3,5-dimethyl-isoxazol-4-yl)phenyl, 3-quinolin-3-ylphenyl, 3-pyridin-3-ylphenyl, 3'-fluorobiphenyl-3-yl, 3'-acetyl-biphenyl-3-yl, 3-(1H-indol-6-yl)phenyl, 3'-hydroxy-biphenyl-3-yl, 4-naphth-1-yl-phenyl, 3'-acetamide-biphenyl-3-yl, 4'-fluorobiphenyl-3-yl, 3-benzo[1,3]dioxol-5-ylphenyl, 4'-methoxycarbonyl-biphenyl-3-yl, 3-(6-methoxy-pyridin-3-yl)phenyl, 3'-methoxycarbonyl-biphenyl-3-yl, 3'-methoxy-biphenyl-3-yl, 4'-methoxy-biphenyl-3-yl, 4'-dimethylamino-biphenyl-4-yl, 2',3',4'-trimethoxy-biphenyl-4-yl, 3-(2,4-dimethoxy-pyrimidin-5-yl)phenyl, 4'-dimethylamino-bi-

phenyl-3-yl, 3',4'-dimethoxy-biphenyl-3-yl, 4-(4-tert-butylthiazol-2-yl)phenyl, 3'-trifluoromethyl-biphenyl-3-yl, 2',3',4'-trimethoxy-biphenyl-3-yl, 3-naphth-1-ylphenyl,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

Still further selected compounds of embodiment A are those in which

R1 is biphenyl-4-yl, 4-(3,5-dimethyl-isoxazol-4-yl)phenyl, 4-thiophen-2-ylphenyl, 4-thiophen-3-yl-phenyl, 4'-fluorobiphenyl-4-yl, 3'-fluorobiphenyl-4-yl, 4-benzo[1,3]dioxol-5-ylphenyl, 4-furan-3-ylphenyl, 3'-carbonitril-biphenyl-4-yl, 4'-methoxy-biphenyl-4-yl, 3'-amino-biphenyl-4-yl, 4-(2,4-dimethoxy-pyrimidin-5-yl)phenyl, 3'-acetyl-biphenyl-4-yl, 4-quinolin-3-ylphenyl, 4'-trifluoromethyl-biphenyl-4-yl, 4-(2-methoxypyridin-3-yl)phenyl, 3',4'-dimethoxy-biphenyl-4-yl, 3'-methoxycarbonyl-biphenyl-4-yl, 3-furan-3-ylphenyl, 4'-methoxycarbonyl-biphenyl-4-yl, 4-(1H-indol-6-yl)phenyl, 3'-trifluoromethyl-biphenyl-4-yl, 3-thiophen-3-ylphenyl, 3'-acetamide-biphenyl-4-yl, 3'-amino-biphenyl-3-yl, 3-furan-2-ylphenyl, 3'-methoxy-biphenyl-4-yl, 3-pyridin-4-ylphenyl, 3'-carbonitril-biphenyl-3-yl, 3-(3,5-dimethyl-isoxazol-4-yl)phenyl, 3-quinolin-3-ylphenyl, 3-pyridin-3-ylphenyl, 3'-fluorobiphenyl-3-yl, 3'-acetyl-biphenyl-3-yl, 3-(1H-indol-6-yl)phenyl, 3'-hydroxy-biphenyl-3-yl, 4-naphth-1-ylphenyl, 3'-acetamide-biphenyl-3-yl, 4'-fluorobiphenyl-3-yl, 3-benzo[1,3]dioxol-5-ylphenyl, 4'-methoxycarbonyl-biphenyl-3-yl, 3-(6-methoxy-pyridin-3-yl)phenyl, 3'-methoxycarbonyl-biphenyl-3-yl, 3'-methoxy-biphenyl-3-yl, 4'-methoxy-biphenyl-3-yl, 4'-dimethylamino-biphenyl-4-yl, 2',3',4'-trimethoxy-biphenyl-4-yl, 3-(2,4-dimethoxy-pyrimidin-5-yl)phenyl, 4'-dimethylamino-biphenyl-3-yl, 3',4'-dimethoxy-biphenyl-3-yl, 4-(4-tert-butylthiazol-2-yl)phenyl, 3'-trifluoromethyl-biphenyl-3-yl, 2',3',4'-trimethoxy-biphenyl-3-yl, 3-naphth-1-ylphenyl,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

Another embodiment (embodiment B) of the compounds of formula 1 are those compounds in which

R1 is 3-7C-cycloalkoxy substituted by R2, R3 and R4,

wherein either

R2 is hydroxyl, cyano, hydroxycarbonyl, trifluoromethyl, 1-4C-alkoxy completely or predominantly substituted by fluorine, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, mono-or di-1-4C-alkylaminosulfonyl, phenoxy, benzyloxy or aryl3,

R3 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino or mono- or di-1-4C-alkylaminocarbonyl,

R4 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

or

R2 is halogen, hydroxyl, cyano, nitro, hydroxycarbonyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy completely or predominantly substituted by fluorine, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonylamino, amino, aminocar-

bonyl, mono- or di-1-4C-alkylamino, mono- or di-1-4C-alkylaminocarbonyl, mono-or di-1-4C-alkylaminosulfonyl, phenoxy, benzyloxy or aryl3,

R3 is 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl or mono- or di-1-4C-alkylaminocarbonyl,

R4 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

aryl2 is phenyl, furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl or triazinyl,

aryl3 is aryl2, aryl2 substituted by R5, R6 and R7, aryl4 or aryl4 substituted by R5, R6 and R7,

aryl4 is a condensed bicyclic ring system - of which at least one ring is aromatic - containing 8 to 10 carbon atoms, which optionally can be replaced by up to four heteroatoms selected from the group consisting of O, N and S,

R5 is halogen, hydroxyl, cyano, nitro, hydroxycarbonyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy completely or predominantly substituted by fluorine, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino, mono- or di-1-4C-alkylaminocarbonyl, mono-or di-1-4C-alkylaminosulfonyl or phenyl,

R6 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino or mono- or di-1-4C-alkylaminocarbonyl,

R7 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

Compounds of embodiment B to be emphasized are those in which

R1 is 3-7C-cycloalkoxy substituted by R2, R3 and R4,

wherein either

R2 is hydroxyl, cyano, hydroxycarbonyl, trifluoromethyl, 1-4C-alkoxy completely or predominantly substituted by fluorine, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, mono-or di-1-4C-alkylaminosulfonyl, phenoxy or benzyloxy,

R3 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

R4 is hydrogen,

or

R2 is halogen, hydroxyl, cyano, nitro, hydroxycarbonyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy completely or predominantly substituted by fluorine, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino, mono- or di-1-4C-alkylaminocarbonyl, mono-or di-1-4C-alkylaminosulfonyl, phenoxy, benzyloxy or aryl3,

R3 is 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl or mono- or di-1-4C-alkylaminocarbonyl,

R4 is hydrogen,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

Further compounds of embodiment B to be emphasized are those in which

R1 is 3-7C-cycloalkyl substituted by R2, R3 and R4,

wherein

R2 is aryl4, aryl2, aryl2 substituted by R5, R6 and R7,

R3 is hydrogen,

R4 is hydrogen,

aryl2 is phenyl, furanyl, thiophenyl, pyrrolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl,

aryl4 is quinolinyl, benzo[1,3]dioxolyl, indolyl or naphthalenyl,

R5 is halogen, hydroxyl, cyano, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonylamino, di-1-4C-alkylamino or amino,

R6 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

R7 is hydrogen or 1-4C-alkoxy,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

Preferred compounds of embodiment B are those in which

R1 is cyclopropyl substituted by R2, R3 and R4,

wherein either

R2 is hydroxyl, cyano, hydroxycarbonyl, trifluoromethyl, 1-4C-alkoxy completely or predominantly substituted by fluorine, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, mono-or di-1-4C-alkylaminosulfonyl, phenoxy or benzyloxy,

R3 is hydrogen,

R4 is hydrogen,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

Further preferred compounds of embodiment B are those in which

R1 is cyclopropyl substituted by R2, R3 and R4,

wherein either

R2 is aryl2, aryl2 substituted by R5, R6 and R7 or aryl4,

R3 is hydrogen,

R4 is hydrogen,

aryl2 is phenyl, furanyl, thiophenyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl or pyrimidinyl,

aryl4 is quinolinyl, benzo[1,3]dioxolyl, indolyl or naphthalenyl,

R5 is halogen, hydroxyl, cyano, 1-4C-alkyl, trifluoromethyl, methoxy, methoxycarbonyl, acetyl, methylcarbonylamino, dimethylamino or amino,

R6 is hydrogen, 1-4C-alkyl or 1-4C-alkoxy,

R7 is hydrogen or 1-4C-alkoxy,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

A selected compound of embodiment B is 2-(2-ethoxycarbonylcyclopropyl)-4,5-dihydro-imidazo-[4,5,1-ij]quinolin-6-one,
and the salts, the N-oxides and the salts of the N-oxides of this compound.

A further embodiment (embodiment C) of the compounds of formula 1 are those compounds
in which

R1 represents a furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl or triazinyl group which is substituted by R2, R3 and R4,

wherein either

R2 is hydroxyl, cyano, hydroxycarbonyl, trifluoromethyl, 1-4C-alkoxy completely or predominantly substituted by fluorine, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, mono-or di-1-4C-alkylaminosulfonyl, phenoxy, benzyloxy or aryl3,

R3 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino or mono- or di-1-4C-alkylaminocarbonyl,

R4 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

or

R2 is halogen, hydroxyl, cyano, nitro, hydroxycarbonyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy completely or predominantly substituted by fluorine, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino, mono- or di-1-4C-alkylaminocarbonyl, mono-or di-1-4C-alkylaminosulfonyl, phenoxy, benzyloxy or aryl3,

R3 is 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl or mono- or di-1-4C-alkylaminocarbonyl,

R4 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

aryl2 is phenyl, furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl or triazinyl,

aryl3 is aryl2, aryl2 substituted by R5, R6 and R7, aryl4 or aryl4 substituted by R5, R6 and R7,

aryl4 is a condensed bicyclic ring system - of which at least one ring is aromatic - containing 8 to 10 carbon atoms, which optionally can be replaced by up to four heteroatoms selected from the group consisting of O, N and S,

R5 is halogen, hydroxyl, cyano, nitro, hydroxycarbonyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy completely or predominantly substituted by fluorine, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino, mono- or di-1-4C-alkylaminocarbonyl, mono-or di-1-4C-alkylaminosulfonyl or phenyl,

R6 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino or mono- or di-1-4C-alkylaminocarbonyl,

R7 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

Compounds of embodiment C to be emphasized are those in which

R1 represents a furanyl, thiophenyl, pyrrolyl, imidazolyl, pyridinyl or pyrimidinyl group which is substituted by R2, R3 and R4,

wherein

R2 is hydroxyl, cyano, hydroxycarbonyl, trifluoromethyl, 1-4C-alkoxy completely or predominantly substituted by fluorine, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, mono-or di-1-4C-alkylaminosulfonyl, phenoxy or benzyloxy,

R3 is hydrogen,

R4 is hydrogen,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

Further compounds of embodiment C to be emphasized are those in which

R1 represents a furanyl, thiophenyl, pyrrolyl, imidazolyl, pyridinyl or pyrimidinyl group which is substituted by R2, R3 and R4,

wherein

R2 is aryl2, aryl2 substituted by R5, R6 and R7 or aryl4,

R3 is hydrogen,

R4 is hydrogen,

aryl2 is phenyl, furanyl, thiophenyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl or pyrimidinyl,

aryl4 is quinolinyl, benzo[1,3]dioxolyl, indolyl or naphthalenyl,

R5 is halogen, hydroxyl, cyano, 1-4C-alkyl, trifluoromethyl, methoxy, methoxycarbonyl, acetyl, methylcarbonylamino, dimethylamino or amino,

R6 is hydrogen, 1-4C-alkyl or 1-4C-alkoxy,

R7 is hydrogen or 1-4C-alkoxy,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

A selected compound of embodiment C is 2-(2,5-dimethyl-1-phenyl-1H-pyrrol-3-yl)-4,5-dihydroimidazo[4,5,1-ij]quinolin-6-one and the salts, the N-oxides and the salts of the N-oxides of this compound.

A further embodiment (embodiment D) of the compounds of formula 1 are the compounds in which

R1 is benzo[1,3]dioxolyl or 1,2,3,4-tetrahydronaphthalenyl,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

A selected compound of embodiment D is 2-([1,3]dioxol-5-yl)-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one and the salts, the N-oxides and the salts of the N-oxides of this compound.

A further embodiment (embodiment E) of the compounds of formula 1 are
2-(Quinolin-2-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(3,4-Dimethoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-Cyclohexyl-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,
2-(4-Methoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(Thiophen-2-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(Pyridin-2-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(3-Hydroxy-4-methoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(3-Fluoro-4-methoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(3-Fluoro-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(1-Methyl-1*H*-pyrrol-2-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(3-Hydroxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(3-Methyl-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-Fluoro-4-methoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(3-Methoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(1*H*-Indol-5-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(3-Cyano-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(1*H*-Imidazol-4-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(Pyridin-3-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(Thiophen-3-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(3-Phenoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(3-Methoxycarbonyl-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(3-Trifluoromethoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(Furan-3-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one and
2-(3-Bromphenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
and the salts, the N-oxides and the salts of the N-oxides of these compounds.

Selected compounds of embodiment E are
2-(Quinolin-2-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(3,4-Dimethoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(4-Methoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(3-Hydroxy-4-methoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(3-Fluoro-4-methoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(3-Fluoro-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(1-Methyl-1*H*-pyrrol-2-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(3-Hydroxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,

2-(3-Methyl-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(2-Fluoro-4-methoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(3-Methoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(1*H*-Indol-5-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(1*H*-Imidazol-4-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(Thiophen-3-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(3-Methoxycarbonyl-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(3-Trifluoromethoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(Furan-3-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one and
2-(3-Bromphenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
and the salts, the N-oxides and the salts of the N-oxides of these compounds.

A further embodiment (embodiment F) of the compounds of formula 1 are
2-(Acetylamino-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(3-Benzyloxy-4-methoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(4-Methansulfonyl-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(3′-Acetamide-biphenyl-4-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(3′-Acetamide-biphenyl-3-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
and the salts, the N-oxides and the salts of the N-oxides of these compounds.

A further aspect of the invention are compounds of formula 1 selected from
2-(Naphthalen-2-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(4-Trifluoromethyl-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(4-Trifluoromethoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-Phenyl-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(3-Chloro-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(4-Bromphenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
and the salts, the N-oxides and the salts of the N-oxides of these compounds for use in the treatment of diseases.

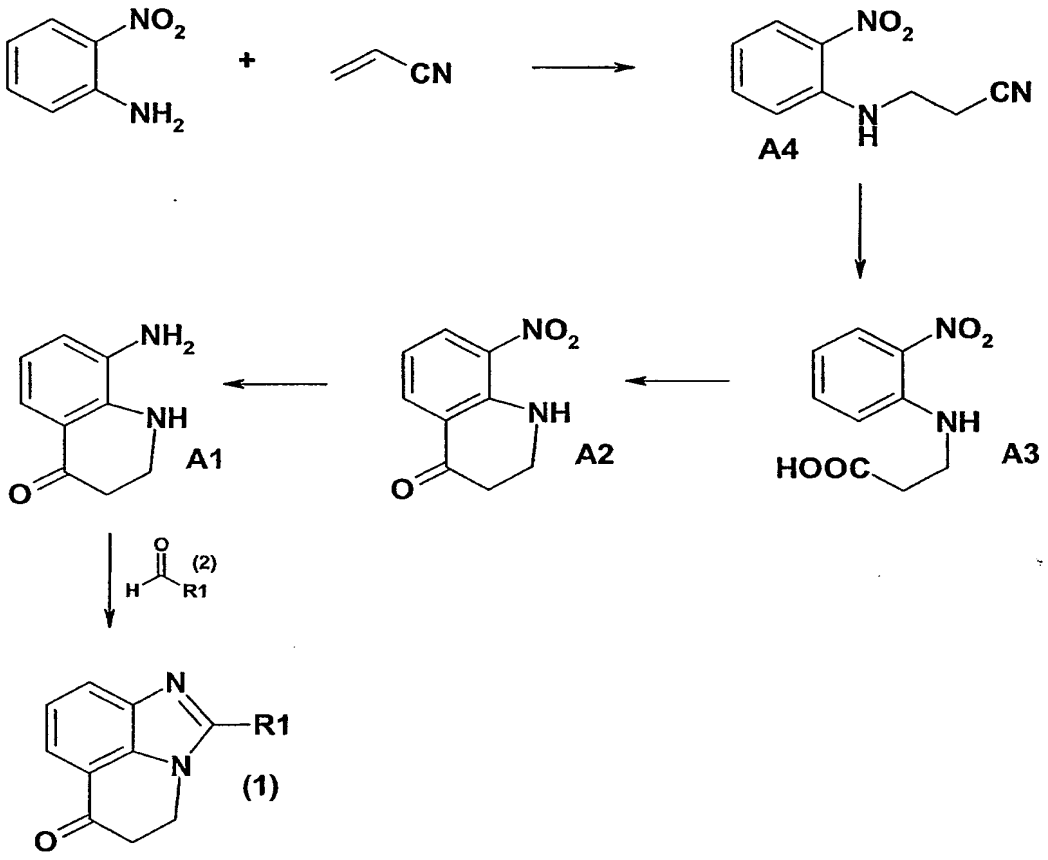
The preparation of the compounds of the formula 1 in which R1 have the meanings indicated above and their salts can be carried out, for example, by the processes described in EP0405442 or EP0638570 or by the process described below (Reaction scheme 1) in greater detail.

In a first step 2-nitroaniline is reacted with acylonitrile to yield 3-(2-nitrophenylamino)propionitrile (compound A4). The propionitrile is then saponified to the corresponding propionic acid (starting compound A3). Cyclocondensation of starting compound A3 results in 2,3-Dihydro-8-nitro-1H-quinolin-4-one (starting compound A2). Selective reduction of the 8-nitro-group yields 2,3-Dihydro-8-amino-1H-quinolin-4-one (starting compound A1).

The compounds of formula 1 are obtained in the final step by reacting starting compound A1 with aldehydes of the formula 2, in which R1 has the above indicated meanings.

Aldehydes of formula 2, in which R1 has the meanings indicated above are known or can be prepared according to methods known to the person skilled in the art.

Reaction scheme 1:



It is known to the person skilled in the art that in the case of a number of reactive centers on a starting or intermediate compound it may be necessary to block one or more reactive centers temporarily by protective groups in order to allow a reaction to proceed specifically at the desired reaction center. A detailed description of the use of a large number of proven protective groups is found, for example, in T.W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991.

In addition, the compounds of the formula 1 can be converted, if desired, into their N-oxides, for example with the aid of hydrogen peroxide in methanol or with the aid of m-chloroperoxybenzoic acid in di-

chloromethane. The person skilled in the art is familiar on the basis of his/her expert knowledge with the reaction conditions which are specifically necessary for carrying out the N-oxidation.

The isolation and purification of the substances according to the invention is carried out in a manner known per se, e.g. by distilling off the solvent in vacuo and recrystallizing the resulting residue from a suitable solvent or subjecting it to one of the customary purification methods, such as, for example, column chromatography on suitable support material.

Salts are obtained by dissolving the free compound in a suitable solvent (e.g. a ketone, such as acetone, methyl ethyl ketone or methyl isobutyl ketone, an ether, such as diethyl ether, tetrahydrofuran or dioxane, a chlorinated hydrocarbon, such as methylene chloride or chloroform, or a low molecular weight aliphatic alcohol such as ethanol or isopropanol) which contains the desired acid or base, or to which the desired acid or base is then added. The salts are obtained by filtering, reprecipitating, precipitating with a nonsolvent for the addition salt or by evaporating the solvent. Salts obtained can be converted by alkalization or by acidification into the free compounds, which in turn can be converted into salts. In this way, pharmacologically intolerable salts can be converted into pharmacologically tolerable salts.

The following examples serve to illustrate the invention further without restricting it. Likewise, further compounds of the formula 1, whose preparation is not explicitly described, can be prepared in an analogous manner or in a manner familiar per se to the person skilled in the art using customary process techniques.

In the examples, h stands for hour(s), RT for room temperature, calc. for calculated, fnd. for found. MS stans for Atmospheric Pressure Chemical Ionisation Mass Spectrometry (APCI-MS) or Electron Impact Ionisation Mass Spectrometry (EI-MS). The compounds mentioned in the examples and their salts are a preferred subject of the invention.

Examples

Final products

1. 2-Cyclohexyl-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one

31.4 mg cyclohexylaldehyde and 32.4 mg starting compound A1 are dissolved in 1400 µl methanol. 140 µl of 2 N aqueous hydrochloric acid and 800 mg silica were added. The mixture was stirred for 16 h at RT and for 3 h at 90°C and evaporated to dryness. The crude product on dry silica is purified by flash chromatography using strong cation exchange silica. Further purification is performed by reversed phase (C18) prep. HPLC to give after evaporation 26.2 mg of the product.

^{1}H-NMR (200MHz, D_6-DMSO): δ = 1.25-1.59 (m, 5H), 1.66-1.86 (m, 4H), 1.94-2.00 (m, 2H), 3.06 (t, 2H), 4.56 (t, 2H), 7.25 (t, 1H), 7.49 (dd, 1H), 7.83 (dd, 1H).

MS: calc: $C_{16}H_{18}N_2O$ (254.33) fnd:[M+1] 255.1 HPLC [min]: 6.03

The following examples are prepared analogously to example 1:

2. 2-Phenyl-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{16}H_{12}N_2O$ (248.29) fnd:[M+HCOOH+1] 295.3 HPLC [min]: 8.29

3. 2-(3-Fluoro-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{16}H_{11}FN_2O$ (266.28) fnd:[M+HCOOH+1] 313.3 HPLC [min]: 8.72

4. 2-(3-Chloro-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{16}H_{11}ClN_2O$ (282.73) fnd:[M+HCOOH+1] 329.3 HPLC [min]: 9.49

5. 2-(3-Cyano-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{17}H_{11}N_3O$ (273.3) fnd:[M+HCOOH+1] 320.2 HPLC [min]: 8.05

6. 2-(3-Methyl-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{17}H_{14}N_2O$ (262.31) fnd:[M+HCOOH+1] 309.3 HPLC [min]: 9.89

7. 2-(3-Hydroxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{16}H_{12}N_2O_2$ (264.29) fnd:[M+HCOOH+1] 311.3 HPLC [min]: 7.41

8. 2-(4-Trifluoromethyl-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{17}H_{11}F_3N_2O$ (316.29) fnd:[M+HCOOH+1] 363.3 HPLC [min]: 10.03

9. 2-(4-Methoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{17}H_{14}N_2O_2$ (278.31) fnd:[M+HCOOH+1] 325.3 HPLC [min]: 8.85

10. 2-(3-Methoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{17}H_{14}N_2O_2$ (278.31) fnd:[M+HCOOH+1] 325.3 HPLC [min]: 9.09

11. 2-(4-Trifluoromethoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{17}H_{11}F_3N_2O_2$ (332.28) fnd:[M+HCOOH+1] 379.3 HPLC [min]: 10.05

12. 2-(3-Trifluoromethoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{17}H_{11}F_3N_2O_2$ (332.28) fnd:[M+HCOOH+1] 379.3 HPLC [min]: 10.27

13. 2-(4-Methylsulfanyl-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{17}H_{14}N_2OS$ (294.38) fnd:[M+HCOOH+1] 341.3 HPLC [min]: 10.61

14. 2-(Biphenyl-4-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{22}H_{16}N_2O$ (324.39) fnd:[M+HCOOH+1] 371.4 HPLC [min]: 11.28

15. 2-(3-Methoxycarbonyl-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{18}H_{14}N_2O_3$ (306.32) fnd:[M+HCOOH+1] 353.3

16. 2-(4-Acetylamino-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{18}H_{15}N_3O_2$ (305.34) fnd:[M+HCOOH+1] 352.3 HPLC [min]: 7.95

17. 2-(4-Methansulfonyl-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{17}H_{14}N_2O_3S$ (326.38) fnd:[M+HCOOH+1] 373.3 HPLC [min]: 6.85

18. 2-(3-Phenoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{22}H_{16}N_2O_2$ (340.39) fnd:[M+HCOOH+1] 387.4 HPLC [min]: 10.67

19. 2-(3,4-Dimethoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{18}H_{16}N_2O_3$ (308.34) fnd:[M+HCOOH+1] 355.3 HPLC [min]: 7.95

20. 2-(3-Hydroxy-4-methoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{17}H_{14}N_2O_3$ (294.31) fnd:[M+HCOOH+1] 341.3 HPLC [min]: 9.2

21. 2-(3-Fluoro-4-methoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{17}H_{13}FN_2O_2$ (296.3) fnd:[M+HCOOH+1] 343.3 HPLC [min]: 8.59

22. 2-(2-Fluoro-4-methoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{17}H_{13}FN_2O_2$ (296.3) fnd:[M+HCOOH+1] 343.3 HPLC [min]: 9.25

23. 2-(3-Benzyloxy-4-methoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{24}H_{20}N_2O_3$ (384.44) fnd:[M+HCOOH+1] 431.3 HPLC [min]: 10.32

24. 2-(2-Ethoxycarbonyl-cyclopropyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{16}H_{16}N_2O_3$ (284.32) fnd:[M+1] 285.3 HPLC [min]: 5.81

25. 2-(Naphthalen-2-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{20}H_{14}N_2O$ (298.35) fnd:[M+HCOOH+1] 345.4 HPLC [min]: 10.51

26. 2-(Quinolin-2-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{19}H_{13}N_3O$ (299.33) fnd:[M+HCOOH+1] 346.3 HPLC [min]: 8.72

27. 2-(Pyridin-3-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{15}H_{11}N_3O$ (249.27) fnd:[M+HCOOH+1] 296.3 HPLC [min]: 6.59

28. 2-(Pyridin-2-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{15}H_{11}N_3O$ (249.27) fnd:[M+HCOOH+1] 296.3 HPLC [min]: 6.27

29. 2-(1*H*-Indol-5-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{18}H_{13}N_3O$ (287.32) fnd:[M+HCOOH+1] 334.5 HPLC [min]: 13.49

30. 2-(Benzo[1,3]dioxol-5-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{17}H_{12}N_2O_3$ (292.3) fnd:[M+HCOOH+1] 339.3 HPLC [min]: 9.36

31. 2-(Thiophen-2-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{14}H_{10}N_2OS$ (254.31) fnd:[M+HCOOH+1] 301.3 HPLC [min]: 7.95

32. 2-(Thiophen-3-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{14}H_{10}N_2OS$ (254.31) fnd:[M+HCOOH+1] 301.3 HPLC [min]: 8.64

33. 2-(Furan-3-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{14}H_{10}N_2O_2$ (238.25) fnd:[M+HCOOH+1] 285.3 HPLC [min]: 7.84

34. 2-(1-Methyl-1*H*-pyrrol-2-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{15}H_{13}N_3O$ (251.29) fnd:[M+HCOOH+1] 298.3 HPLC [min]: 9.01

35. 2-(1*H*-Imidazol-4-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{13}H_{10}N_4O$ (238.25) fnd:[M+HCOOH+1] 285.3 HPLC [min]: 8.88

36. 2-(2,5-Dimethyl-1-phenyl-1*H*-pyrrol-3-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{22}H_{19}N_3O$ (341.42) fnd:[M+HCOOH+1] 388.4 HPLC [min]: 12.67

37. 2-(4-Bromphenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{16}H_{11}BrN_2O$ (327.18) fnd:[M+1] 327.2; 329.2 HPLC [min]: 7.20

38. 2-(3-Bromphenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{16}H_{11}BrN_2O$ (327.18) fnd:[M+1]327.2; 329.2 HPLC [min]: 7.25

39. 2-(4-Pyridin-2-yl-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

32.7 mg of the compound of example **37** and 27.1 mg 2-pyridin boronic acid are dissolved in dimethoxyethane under an atmosphere of nitrogen. $Pd(PPh_3)_4$ and 250 µl of a 2N aqueous solution of sodium carbonate is added and the mixture is stirred for 15 h at 75°C. The reaction mixture is cooled to RT, 4 ml of water and 12 ml of dichloromethane are added and the organic layer is separated. After evaporation the product is purified by flash chromatography to yield 25.5 mg.

^{1}H-NMR (200 MHz, D_6-DMSO): □= 3.13 (t, J=6.9Hz,2H), 4.86 (t, J=6.9Hz,2H), 7.35-7.42 (m,2H), 7.62 (d,J=7.0Hz,1H), 7.90-7.97 (m,2H), 8.07-8.14 (m,4H), 8.32 (d,J=8.4Hz,1H), 8.73 (d,J=4.0Hz,1H).

MS: calc: $C_{21}H_{15}N_3O$ (325.37) fnd:[M+1] 326.3 HPLC [min]: 7.25

The following examples are prepared analogously to example **39** using the compound of example **37** or **38**, respectively, as starting materials:

40. 2-(4-Pyridin-4-yl-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{21}H_{15}N_3O$ (325.37) fnd:[M+1] 326.2 HPLC [min]: 6.72

41. 2-(4-Pyridin-3-yl-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{21}H_{15}N_3O$ (325.37) fnd:[M+1] 326.2 HPLC [min]: 6.64

42. 2-[4-(3,5-Dimethyl-isoxazol-4-yl)-phenyl)]-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{21}H_{17}N_3O_2$ (343.39) fnd:[M+1] 344.1 HPLC [min]: 6.85

43. 2-(4-Thiophen-2-yl-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{20}H_{14}N_2OS$ (330.41) fnd:[M+1] 331.1 HPLC [min]: 7.79

44. 2-(4-Thiophen-3-yl-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{20}H_{14}N_2OS$ (330.41) fnd:[M+1] 331.1 HPLC [min]: 7.68

45. 2-(4′-Fluoro-biphenyl-4-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{22}H_{15}FN_2O$ (342.38) fnd:[M+1] 343.1 HPLC [min]: 8.03

46. 2-(3′-Fluoro-biphenyl-4-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{22}H_{15}FN_2O$ (342.38) fnd:[M+1] 343.1 HPLC [min]: 8.03

47. 2-(4-Benzo[1,3]dioxol-5-yl-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{23}H_{16}N_2O_3$ (368.4) fnd:[M+1] 369.2 HPLC [min]: 7.73

48. 2-(4-Furan-3-yl-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{20}H_{14}N_2O_2$ (314.35) fnd:[M+1] 315.1 HPLC [min]: 7.25

49. 2-(3′-Carbonitril-biphenyl-4-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{23}H_{15}N_3O$ (349.4) fnd:[M+1] 350.2 HPLC [min]: 6.93

50. 2-(4′-Methoxy-biphenyl-4-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{23}H_{18}N_2O_2$ (354.41) fnd:[M+1] 355.1 HPLC [min]: 7.89

51. 2-(3′-Amino-biphenyl-4-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{22}H_{17}N_3O$ (339.4) fnd:[M+1] 340.2 HPLC [min]: 6.83

52. 2-[4-(2,4-Dimethoxy-pyrimidin-5-yl)-phenyl]-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{22}H_{18}N_4O_3$ (386.41) fnd:[M+1] 387.1 HPLC [min]: 7.04

53. 2-(3′-Acetyl-biphenyl-4-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{24}H_{18}N_2O_2$ (366.42) fnd:[M+1] 367.2 HPLC [min]: 7.41

54. 2-(4-Quinolin-3-yl-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{25}H_{17}N_3O$ (375.43) fnd:[M+1] 376.2 HPLC [min]: 7.79

55. 2-(4′-Trifluormethyl-biphenyl-4-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{23}H_{15}F_3N_2O$ (392.38) fnd:[M+1] 393.2 HPLC [min]: 8.67

56. 2-[4-(2-Methoxy-pyridin-3-yl)-phenyl]-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{22}H_{17}N_3O_2$ (355.4) fnd:[M+1] 356.1 HPLC [min]: 7.28

57. 2-(3′,4′-Dimethoxy-biphenyl-4-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{24}H_{20}N_2O_3$ (384.44) fnd:[M+1] 385.2 HPLC [min]: 7.39

58. 2-(3′-Carboxylic-acid-methylester-biphenyl-4-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{24}H_{18}N_2O_3$ (382.42) fnd:[M+1] 383.1 HPLC [min]: 7.87

59. 2-(3-Furan-3-yl-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{20}H_{14}N_2O_2$ (314.35) fnd:[M+1] 315.1 HPLC [min]: 7.36

60. 2-(4′-Carboxylic-acid-methylester-biphenyl-4-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{24}H_{18}N_2O_3$ (382.42) fnd:[M+1] 383.1 HPLC [min]: 7.81

61. 2-[4-(1H-Indol-6-yl)-phenyl]-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{24}H_{17}N_3O$ (363.42) fnd:[M+1] 364.1 HPLC [min]: 7.55

62. 2-(3´-Trifluormethyl-biphenyl-4-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{23}H_{15}F_3N_2O$ (392.38) fnd:[M+1] 393.2 HPLC [min]: 8.67

63. 2-(3-Thiophen-3-yl-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{20}H_{14}N_2OS$ (330.41) fnd:[M+1] 331.1 HPLC [min]: 7.76

64. 2-(3´-Acetamide-biphenyl-4-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{24}H_{19}N_3O_2$ (381.43) fnd:[M+1] 382.2 HPLC [min]: 6.59

65. 2-(3´-Amino-biphenyl-3-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{22}H_{17}N_3O$ (339.4) fnd:[M+1] 340.1 HPLC [min]: 7.65

66. 2-(3-Furan-2-yl-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{20}H_{14}N_2O_2$ (314.35) fnd:[M+1] 315.1 HPLC [min]: 7.52

67. 2-(3´-Methoxy-biphenyl-4-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{23}H_{18}N_2O_2$ (354.41) fnd:[M+1] 355.2 HPLC [min]: 7.89

68. 2-(3-Pyridin-4-yl-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{21}H_{15}N_3O$ (325.37) fnd:[M+1] 326.2 HPLC [min]: 6.88

69. 2-(Biphenyl-4-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{22}H_{16}N_2O$ (324.39) fnd:[M+1] 325.5 HPLC [min]: 11.28

70. 2-(3´-Carbonitril-biphenyl-3-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{23}H_{15}N_3O$ (349.4) fnd:[M+1] 350.2 HPLC [min]: 7.68

71. 2-[3-(3,5-Dimethyl-isoxazol-3-yl)-phenyl)]-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{21}H_{17}N_3O_2$ (343.39) fnd:[M+1] 344.1 HPLC [min]: 6.91

72. 2-(3-Quinolin-3-yl-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{25}H_{17}N_3O$ (375.43) fnd:[M+1] 376.2 HPLC [min]: 7.73

73. 2-(3-Pyridin-3-yl-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{21}H_{15}N_3O$ (325.37) fnd:[M+1] 326.1 HPLC [min]: 6.69

74. 2-(3´-Fluoro-biphenyl-3-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{22}H_{15}FN_2O$ (342.38) fnd:[M+1] 343.2 HPLC [min]: 8.32

75. 2-(3´-Acetyl-biphenyl-3-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{24}H_{18}N_2O_2$ (366.42) fnd:[M+1] 367.2 HPLC [min]: 7.63

76. 2-[3-(1H-Indol-6-yl)-phenyl]-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{24}H_{17}N_3O$ (363.42) fnd:[M+1] 364.2 HPLC [min]: 7.57

77. 2-(3´-Acetyl-biphenyl-3-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{24}H_{18}N_2O_2$ (366.42) fnd:[M+1] 367.2 HPLC [min]: 7.60

78. 2-(3´-Hydroxy-biphenyl-3-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{22}H_{16}N_2O_2$ (340.39) fnd:[M+1] 341.2 HPLC [min]: 5.44

79. 2-(4-Naphth-1-ylphenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{26}H_{18}N_2O$ (374.45) fnd:[M+1] 375.2 HPLC [min]: 8.75

80. 2-(3´-Acetamide-biphenyl-3-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{24}H_{19}N_3O_2$ (330.41) fnd:[M+1] 382.1 HPLC [min]: 6.67

81. 2-(4´-Fluoro-biphenyl-3-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{22}H_{15}FN_2O$ (342.38) fnd:[M+1] 343.3 HPLC [min]: 8.32

82. 2-(3-Benzo[1,3]dioxol-5-yl-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{23}H_{16}N_2O_3$ (368.4) fnd:[M+1] 369.2 HPLC [min]: 8.05

83. 2-(4´-Carboxylic-acid-methylester-biphenyl-3-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{24}H_{18}N_2O_3$ (382.42) fnd:[M+1] 383.2 HPLC [min]: 7.92

84. 2-[3-(6-Methoxy-pyridin-3-yl)-phenyl]-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{22}H_{17}N_3O_2$ (355.4) fnd:[M+1] 356.2 HPLC [min]: 7.41

85. 2-(3´-Carboxylic-acid-methylester-biphenyl-3-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{24}H_{18}N_2O_3$ (382.42) fnd:[M+1] 383.1 HPLC [min]: 7.92

86. 2-(3´-Methoxy-biphenyl-3-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{23}H_{18}N_2O_2$ (354.41) fnd:[M+1] 355.2 HPLC [min]: 8.19

87. 2-(4´-Methoxy-biphenyl-3-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{23}H_{18}N_2O_2$ (354.41) fnd:[M++1] 355.2 HPLC [min]: 8.16

88. 2-(4´-Dimethylamino-biphenyl-4-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{24}H_{21}N_3O$ (367.45) fnd:[M+1] 368.2 HPLC [min]: 8.21

89. 2-(2′,3′,4′-Trimethoxy-biphenyl-4-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{25}H_{22}N_2O_4$ (414.47) fnd:[M+1] 415.2 HPLC [min]: 7.49

90. 2-[3-(2,4-Dimethoxy-pyrimidin-5-yl)-phenyl]-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{22}H_{18}N_4O_3$ (386.41) fnd:[M+1] 387.2 HPLC [min]: 7.09

91. 2-(4′-Dimethylamino-biphenyl-3-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{24}H_{21}N_3O$ (367.45) fnd:[M+1] 368.3 HPLC [min]: 8.53

92. 2-(3′,4′-Dimethoxy-biphenyl-3-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{24}H_{20}N_2O_3$ (384.44) fnd:[M+1] 385.1 HPLC [min]: 7.47

93. 2-[4-(4-*tert*-Butyl-thiazol-2-yl)-phenyl]-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{23}H_{21}N_3OS$ (387.51) fnd:[M+1] 388.3

94. 2-(3′-Trifluormethyl-biphenyl-3-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{23}H_{15}F_3N_2O$ (392.38) fnd:[M+1] 393.2 HPLC [min]: 9.01

95. 2-(2′,3′,4′-Trimethoxy-biphenyl-3-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{25}H_{22}N_2O_4$ (414.47) fnd:[M+1] 415.1 HPLC [min]: 7.55

96. 2-(3-Naphth-1-ylphenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one

MS: calc: $C_{26}H_{18}N_2O$ (374.45) fnd:[M+1] 375.2 HPLC [min]: 8.77

Starting compounds

A1. 2,3-Dihydro-8-amino-1*H*-quinolin-4-one

8.6 g 2,3-Dihydro-8-nitro-1*H*-quinolin-4-one (A2) is dissolved in 600 ml methanol and 0.85 g Pd/C (10%) is added under an atmosphere of nitrogen. The mixture is hydrogenated under atmospheric pressure for 16 h. The mixture is filtered over celite and evaporated to dryness. The residue is purified by flash chromatograpy to yield 5.95 g of the title compound.

^{1}H-NMR (200MHz, D_6-DMSO): δ = 2.45-2.52 (m,2H), 3.41-3.49 (m,2H), 4.75 (s, 2H), 5.83 (s,1H), 6.42 (t, 1H), 6.67 (dd, 1H), 6.98 (dd,1H).

A2. 2,3-Dihydro-8-nitro-1*H*-quinolin-4-one

A mixture of 21.0 g 3-(2-nitrophenylamino)-propionic acid (A3) and 42.5 g phosphorus pentoxide in 300 ml abs. toluene is heated at reflux for 2 h. The mixture is filtered and the residue extracted three times with 300 ml of boiling ethyl acetate. The filtrates and extracts are evaporated to dryness to give 10.9 g of the desired product.

^{1}H-NMR (200MHz, D_6-DMSO): δ = 2.70 (t, 2H), 3.62-3.75 (m, 2H), 6.74 (t, 1H), 8.04 (dd, 1H), 8.30 (dd, 1H), 8.61 (s, 1H).

A3. 3-(2-Nitrophenylamino)propionic acid

66.0 g 3-(2-nitrophenylamino)-propionitrile (A4) are suspended in 500 ml 10% KOH and stirred at 130°C für 1.5 h. The clear orange solution is cooled and brought to pH=3 with conc. HCl. After cooling the yellow precipitate is filtered off, washed with water and dried, yielding 63 g.

^{1}H-NMR (200MHz, D_6-DMSO): δ = 2.61 (t, 2H), 3.58 (q, 2H), 6.63-6.72 (m, 1H), 7.09 (dd, 1H), 7.49-7.60 (m, 1H), 8.08 (dd, 1H), 8.19 (t, 1H).

A4. 3-(2-Nitrophenylamino)propionitrile

A solution of 104 g of 2-nitroaniline and 15 ml of Triton B in 500 ml abs ethanol is heated to 80°C and 140 ml acrylonitrile are addded over a period of 5 h. Stirring at 80°C is continued for 24 h. EtOH is removed in vacuo, the oily residue dissolved in 300 ml ethyl acetate, treated with charcoal and 400 ml petrolether are added. After cooling coarse brown crystals are filtered off, yielding 61 g of the desired product.

^{1}H-NMR (200MHz, D_6-DMSO): δ = 2.89 (t, 2H), 3.72 (q, 2H), 6.70-6.78 (m, 1H), 7.18 (dd, 1H), 7.49-7.50 (m, 1H), 8.07 (dd, 1H), 8,25 (t, 1H).

Determination of HPLC-Values

A Superspher 60 RP-Select B 75 x 4 mm column from Merck was used; the chromatography was carried out at a column temperature of 40°C using a flow of 1 ml/min. The solvent system employed was solvent A (water) and solvent B (acetonitrile), with the following gradient course being used:

min	%A	%B
0.0	80	20
1.0	80	20
8.0	20	80
12.0	20	80
15.0	80	20
16.0	80	20

Detection was carried out by UV at 220 nm.

Commercial applicability

The compounds according to the invention have valuable pharmacological properties which make them commercially utilizable. They are inhibitors of the Poly(ADP-ribose)polymerase enzymes, in particular of the PARP-1 isoenzyme. Poly(ADP-ribose) polymerases (PARP, also called PARS, NAD^+-ADP-ribosyl-trans-ferase, pADPRT(EC 2.4.2.30)) are enzymes located in the nuclei of cells of various organs, including muscle, heart, brain and pancreatic cells. PARPs poly-ADP-ribosylate various nuclear proteins and also show auto-poly-ADP-ribosylating properties. PARPs play a physiological role in the maintainance of genomic integrity and stability. While till the late nineties only one PARP-enzyme was known, it is now clear that a whole family of related enzymes exists. Up to now the PARP-family consists of 7 isoenzymes showing high to moderate sequence homologies. High overall homology is found between the isoenzymes PARP-1 to PARP-3. The other isoforms display relevant homologies only at the catalytic site while the other domains of the proteins are completely different. The exact functions of most isoenzymes are not yet known, but it is clear that PARP-1 is physiologically involved in DNA-repair *(Ikai et al., J. Histochem. Cytochem. 11: 1261-1264, 1983)* and transcriptional regulation. PARP-1 is highly expressed in the nuclei of cells and is a member of the base excision repair complex (BER-complex). Once activated by damaged DNA fragments, PARP-1 catalyzes the attachment of up to 100 ADP-ribose units to a variety of nuclear proteins which are involved in DNA repair, including histones, topoisomerases, DNA-polymerases, DNA-ligases and PARP-1 itself. NAD is used as a source of ADP-ribose. Poly–ADP-ribosylation is thought to stabilize the region of the single strand break and to allow the recruitment of other DNA-repair enzymes. Consumed NAD is regenerated by the use of 4 ATP-molecules for every molecule of NAD. After intense auto-ADR-ribosylation PARP-1 becomes negatively charged and dissociates from the DNA.

A high number of DNA strand breaks caused by inflammatory mediators, ischemia/ reperfusion or other stimuli leads to a massive overactivation of PARP-1. It has been shown that overactivation of PARP's especially PARP-1 leads to an immediate consumption of cellular NAD. Thus, intracellular NAD, the substrate of PARP, and ATP are depleted by massive PARP activation and this energy depletion is thought to be one stimulus leading to cellular damage and cell death.

It is well known that temporary oxygen deprivation as found in situations of ischemia and reperfusion leads to the generation of reactive oxygen species which alone or in combination with nitric oxide lead to massive DNA strand breaks. In an effort to repair these strand breaks PARP-1 is overactivated, resulting in cellular NAD and ATP depletion, cell death and organ damage. In isolated organ systems such as heart or skeletal muscle PARP inhibition diminishes ischemia/reperfusion induced tissue damage *(Thiemerman et al. PNAS 94,: 679-683, 1997)* and contractile dysfunction *(Docherty et al. Br. J. Pharmacol. 127,: 1518-1524, 1999)*. Protection from PARP mediated cell death has been shown in PARP-1 knock-out mice in various in-vivo models of cerebral and myocardial ischemia/reperfusion injury. A massive reduction of the necrotic area in the CNS was reported in PARP-1-knock out mice after transient occlusion of the middle cerebral artery. Protection from myocardial ischemia/reperfusion

damage was also seen in PARP-1 knock out mice after transient coronary occlusion. In models of cardiac ischemia and myocardial infarction PARP inhibitors reduce infarct size. It has been shown in myocytes that PARP inhibition inhibits cellular oxydative damage *(Bowes et al. Br. J. Pharmacol. 124: 1760-1766, 1998).*

Similarly, in models of retinal ischemia/reperfusion PARP inhibition has been shown to reduce cellular and organ damage. Confirming results are available from small molecule inhibitors of PARPs in models of transient cerebral ischemia and transient retinal ischemia *(Lam, Res. Com. Mol. Pathol. Pharmacol. 95, 241-252, 1997).*

Similarly, acute or chronic inflammation in general is characterised among others by massive generation of reactive oxygen species and nitric oxide. As in the case of ischemia/reperfusion these reactive species lead to DNA strand breaks, PARP-1 overactivation and cell death. It has been shown that PARP inhibition by small molecule inhibitors or genetic knock out reduces edema formation after zymosan or carrageenan, inhibits cellular damage in pancreatic islet cells after streptozotocin, inhibits experimental arthritis and reduces intestinal damage in models of intestinal inflammation. Evidence exists that PARP inhibitors are useful for treating inflammatory bowel disorders. *(Salzman et al., Japanese J. Pharm., 75, Supp. I:15, 1997).* In rodent in vivo models experimentally induced colitis was reduced by administration of PARP inhibitors.

Evidence also exists that PARP inhibitors are useful for treating arthritis. *(Szabo et al., Japanese J. Pharm., 75, Supp. I:102, 1997).* Beside an inhibition of cellular damage due to the above mentioned mechanisms it has been demonstrated that PARP inhibition reduces the expression of proinflammatory adhesion molecules such as ICAM-1 and P-selectin.

It has also been reported that PARP activation plays a key role in glutamate-, NMDA-, NO-, reactive oxygen species- and glucose deprivation induced neurotoxicity. The use of PARP inhibitors was reported to prevent neurotoxicity in cortical or cerebellar granule cell cultures and in hippocampal slices *(Wallis et al., NeuroReport, 5:3, 245-48. 1993; Cosi et al, J. Neurosci. Res 39: 38-46, 1994; Eliasson et al. Nature Med. 3: 1089-1095, 1997)*; Inhibition of neurotoxicity by various compounds was found to correspond to their PARP-1 inhibitory potency *(Zhang et al., Science, 263:687-89, 1994)*; Excessive activation of glutamate receptors has been implicated in various neurological diseases. NO together with reactive oxygen species has been shown to be causally involved in in-vivo models for various neurodegenerative diseases of the CNS. During ischemia/reperfusion injury various neurotoxic species including glutamate, NO, reactive oxygen species and others are released leading to massive organ damage. Other pathophysiological stimuli resulting in PARP activation and concomittant cell damage are 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), leading to experimental parkinsonism, immune complexes mediating experimental encephalomyelitis and traumatic head injury.

There are also data showing that PARP inhibitors reduce the severity of septic or hemorrhagic shock in animal models. Survival of mice after a lethal dose of LPS was increased by PARP inhibitors *(Szabo et al. Int. J. Oncology 10, 1093-1101, 1997)*. In addition organ dysfunction (shown for lung, liver, intestine) after zymosan in experimental models of shock is reduced by PARP inhibitors *(Szabo et al. J.Exp. Med. 186, 1041-1049, 1997)*.

It has also been shown that PARP-1 inhibition protects pancreatic islet cells from NO or reactive oxygene species induced damage *(Uchigata et al. J. Biol. Chem. 257 6084- 6088,1982)*. In more complex models of streptozotocin induced diabetes, PARP-1 inhibition reduced cellular damage and increased insulin production *(Uchigata et al. Diabetes 32, 316-318, 1983)*

PARP inhibitors have been reported to be effective in radiosensitizing hypoxic tumor cells and in preventing tumor cells from recovering from potentially lethal damage of DNA after radiation therapy, presumably by their ability to prevent DNA repair *(Griffin et al. J. Med. Chem. 41, 5247-5256, 1998)*.

On account of their PARP - in particular their PARP-1 - inhibiting properties, the compounds according to the invention can be employed in human and veterinary medicine and therapeutics, where they can be used for the treatment and prophylaxis of the following diseases: vascular stroke (cerebral stroke), myocardial infarction and other cardiovascular disorders (artherosclerosis), diabetes, head trauma, sepsis and septic shock; hemorrhagic shock, tissue damage resulting from PARP-1 mediated necrosis or apoptosis; any kind of reperfusion injury; especially neuronal (CNS), myocardial, retinal or other tissue damage resulting from ischemia and reperfusion; ischemia/reperfusion injury during organ transplantation surgery, surgery with transient interruption of blood flow to organs or body areas, and surgery when heart-lung/heart-circulation machines are used; renal failure due to ischemia or glomerulonephritis, retinal ischemia; neurological disorders and neurodegenerative diseases caused by free radical generation or other PARP-1 activating stimuli; pancreatic disorders; acute and chronic inflammatory diseases (chronic inflammatory disease of the CNS (Alzheimer, multiple sklerosis, Parkinson´s disease), chronic inflammatory diseases of the gastrointestinal tract (Morbus Crohn, colitis ulcerosa), chronic inflammatory diseases of the lungs (acute lung injury, ARDS), chronic inflammatory diseases of the joints (rheumatoid arthritis, osteoarthritis), acute inflammatory diseases of various organs; traumata of various organs; viral infections which rely on PARP-activity for successful DNA integration; infections by human immune deficiency and other viruses (AIDS); degenerative diseases of skeletal muscle involving replicative senescence, immune senescence, muscular dystrophy, chronic and acute pain (neuropathic pain),and skin aging.

In addition to this, conditions including epilepsy, stroke, Alzheimer's disease, Parkinson's disease, Amyotrophic Lateral Sclerosis (ALS), Huntington's disease, schizophrenia, chronic pain, ischemia and neuronal loss following hypoxia, hypoglycemia, ischemia, trauma, and nervous insult can be expected to be mitigated by PARP-1 inhibition. Recent studies have also advanced a glutamatergic basis for compulsive disorders, particularly drug dependence.

Furthermore PARP-inhibitors can be used to extend the lifespan and proliferative capacity of cells; to alter gene expression of senescent cells and to enhance the efficacy of chemo- or radiotherapy in cancers. PARP-inhibitors can also be used to potentiate cellular necrosis and/or apoptosis by chemotherapeutic compounds of various classes.

The invention further relates to a method for the treatment of mammals, including humans, which are suffering from one of the abovementioned illnesses. The method is characterized in that a therapeutically active and pharmacologically effective and tolerable amount of one or more of the compounds according to the invention is administered to the ill mammal.

The invention further relates to the compounds according to the invention for use in the treatment and/or prophylaxis of illnesses, especially the illnesses mentioned.

The invention also relates to the use of the compounds according to the invention for the production of pharmaceutical compositions which are employed for the treatment and/or prophylaxis of the illnesses mentioned.

The invention furthermore relates to pharmaceutical compositions for the treatment and/or prophylaxis of the illnesses mentioned, which contain one or more of the compounds according to the invention.

The pharmaceutical compositions are prepared by processes which are known per se and familiar to the person skilled in the art. As pharmaceutical compositions, the compounds according to the invention (= active compounds) are either employed as such, or preferably in combination with suitable pharmaceutical auxiliaries and/or excipients, e.g. in the form of tablets, coated tablets, capsules, caplets, suppositories, patches (e.g. as TTS), emulsions, suspensions, gels or solutions, the active compound content advantageously being between 0.1 and 95% and where, by the appropriate choice of the auxiliaries and/or excipients, a pharmaceutical administration form (e.g. a delayed release form or an enteric form) exactly suited to the active compound and/or to the desired onset of action can be achieved.

The person skilled in the art is familiar with auxiliaries or excipients which are suitable for the desired pharmaceutical formulations on account of his/her expert knowledge. In addition to solvents, gel formers, ointment bases and other active compound excipients, for example antioxidants, dispersants, emulsifiers, preservatives, solubilizers, colorants, complexing agents or permeation promoters, can be used.

The administration of the pharmaceutical compositions according to the invention may be performed in any of the generally accepted modes of administration available in the art. Illustrative examples of suit-

able modes of administration include intravenous, oral, nasal, parenteral, topical, transdermal and rectal delivery. Oral and intravenous delivery is preferred.

The pharmaceutical compositions according to the invention are prepared by processes known per se. Dosage of the active compounds takes place in the order of magnitude customary for PARP inhibitors. Thus topical application forms (such as, for example, ointments) contain the active compounds in a concentration of, for example, 0.1-99%. For oral administration, e.g., the dosage that may be employed is from about 0.1 to about 100 mg/kg body weight, with courses of treatment repeated at appropriate intervals.

Biological investigations

The potency of the compounds according to the invention to inhibit PARP-1 activity is tested by measuring the auto-ADP-ribosylation reaction at the level of partially purified human PARP-1. Cellular PARP-activity was measured by quantification of nuclear poly-ADP-ribose polymer.

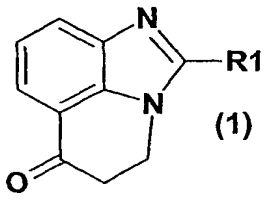
Measurement of enzymatic PARP-1 activity

100 ng of a crude cytosolic fraction of Sf9-cells expressing PARP-1 are incubated in a total volume of 200 µl in the presence of 100 mM Tris/HCl pH 7.4, 1 µM NAD, 1.5 µg Oligonucleotide (GGAATTCC) and 100000 to 200000 dpm of [^{3}H]NAD for various times. Radiolabelled poly-ADP-ribose is measured by adding 50 to 500 ng of an anti polyADP-ribose antibody or an anti-PARP-1 antibody linked to scintillation proximity beads (Protein-A-beads, Amersham-Pharmacia). Bead bound radioactivity is measured in a Wallac Trilux Microbeta counter. Inhibition of PARP activity by compounds is calculated from control values in the absence of compounds and IC_{50}-values (concentration of compound yielding 50 % inhibition) are generated by nonlinear least square fitting.

The inhibitory values [measured as -logIC_{50} (mol/l)] determined for the compounds 1 to 96 according to the invention are all about 5 or greater.

Patent claims

1. Compounds of the formula 1



(1)

in which

R1 is aryl1, aryl1 substituted by R2, R3 and R4, 3-7C-cycloalkyl, 3-7C-cycloalkyl substituted by R2, R3 and R4, or aryl4,

R2 is halogen, hydroxyl, cyano, nitro, hydroxycarbonyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy completely or predominantly substituted by fluorine, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino, mono- or di-1-4C-alkylaminocarbonyl, mono-or di-1-4C-alkylaminosulfonyl, phenoxy, benzyloxy or aryl3,

R3 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino or mono- or di-1-4C-alkylaminocarbonyl,

R4 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

aryl1 is phenyl, furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl or triazinyl,

aryl2 is phenyl, furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl or triazinyl,

aryl3 is aryl2, aryl2 substituted by R5, R6 and R7, aryl4 or aryl4 substituted by R5, R6 and R7,

aryl4 is a condensed bicyclic ring system - of which at least one ring is aromatic - containing 8 to 10 carbon atoms, which optionally can be replaced by up to four heteroatoms selected from the group consisting of O, N and S,

R5 is halogen, hydroxyl, cyano, nitro, hydroxycarbonyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy completely or predominantly substituted by fluorine, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino, mono- or di-1-4C-alkylaminocarbonyl, mono-or di-1-4C-alkylaminosulfonyl or phenyl,

R6 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino or mono- or di-1-4C-alkylaminocarbonyl,

R7 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

and the salts, the N-oxides and the salts of the N-oxides of these compounds for use in the treatment of diseases.

2. Use of compounds of formula 1 in which

R1 is aryl1, aryl1 substituted by R2, R3 and R4, 3-7C-cycloalkyl, 3-7C-cycloalkyl substituted by R2, R3 and R4, or aryl4,

R2 is halogen, hydroxyl, cyano, nitro, hydroxycarbonyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy completely or predominantly substituted by fluorine, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino, mono- or di-1-4C-alkylaminocarbonyl, mono-or di-1-4C-alkylaminosulfonyl, phenoxy, benzyloxy or aryl3,

R3 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino or mono- or di-1-4C-alkylaminocarbonyl,

R4 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

aryl1 is phenyl, furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl or triazinyl,

aryl2 is phenyl, furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl or triazinyl,

aryl3 is aryl2, aryl2 substituted by R5, R6 and R7, aryl4 or aryl4 substituted by R5, R6 and R7,

aryl4 is a condensed bicyclic ring system - of which at least one ring is aromatic - containing 8 to 10 carbon atoms, which optionally can be replaced by up to four heteroatoms selected from the group consisting of O, N and S,

R5 is halogen, hydroxyl, cyano, nitro, hydroxycarbonyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy completely or predominantly substituted by fluorine, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino, mono- or di-1-4C-alkylaminocarbonyl, mono-or di-1-4C-alkylaminosulfonyl or phenyl,

R6 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino or mono- or di-1-4C-alkylaminocarbonyl,

R7 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

and the salts, the N-oxides and the salts of the N-oxides of these compounds for the preparation of pharmaceutical compositions for the treatment of diseases which can be ameliorated by the administration of PARP inhibitors.

3. Compounds of formula 1 in which

R1 is phenyl substituted by R2, R3 and R4,

wherein either

R2 is 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkylcarbonylamino, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, mono-or di-1-4C-alkylaminosulfonyl, benzyloxy or aryl3,

R3 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino or mono- or di-1-4C-alkylaminocarbonyl and

R4 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

or

R2 is halogen, hydroxyl, cyano, nitro, hydroxycarbonyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy completely or predominantly substituted by fluorine, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino, mono- or di-1-4C-alkylaminocarbonyl, mono-or di-1-4C-alkylaminosulfonyl, phenoxy, benzyloxy or aryl3,

R3 is 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkylcarbonylamino, aminocarbonyl or mono- or di-1-4C-alkylaminocarbonyl and

R4 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

aryl2 is phenyl, furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl or triazinyl,

aryl3 is aryl2, aryl2 substituted by R5, R6 and R7, aryl4 or aryl4 substituted by R5, R6 and R7,

aryl4 is a condensed bicyclic ring system - of which at least one ring is aromatic - containing 8 to 10 carbon atoms, which optionally can be replaced by up to four heteroatoms selected from the group consisting of O, N and S,

R5 is halogen, hydroxyl, cyano, nitro, hydroxycarbonyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy completely or predominantly substituted by fluorine, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino, mono- or di-1-4C-alkylaminocarbonyl, mono-or di-1-4C-alkylaminosulfonyl or phenyl,

R6 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino or mono- or di-1-4C-alkylaminocarbonyl,

R7 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

4. Compounds of formula 1 according to claim 3 in which

R1 is phenyl substituted by R2, R3 and R4,

wherein either

R2 is 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkylcarbonylamino or benzyloxy,

R3 is hydrogen, halogen, 1-4C-alkyl, 1-4C-alkoxy, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino or mono- or di-1-4C-alkylaminocarbonyl and

R4 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

or

R2 is hydroxyl, cyano, nitro, hydroxycarbonyl, trifluoromethyl, 1-4C-alkoxy completely or predominantly substituted by fluorine, 1-4C-alkylcarbonyl or benzyloxy,

R3 is 1-4C-alkylthio, 1-4C-alkylsulfonyl or 1-4C-alkylcarbonylamino and

R4 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

and the salts, the N-oxides and the salts of the N-oxides of these compounds

5. Compounds of formula 1 according to claim 3 in which

R1 is phenyl substituted by R2, R3 and R4,

wherein either

R2 is 1-4C-alkylthio, 1-4C-alkylsulfonyl or 1-4C-alkylcarbonylamino,

R3 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy and

R4 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

or

R2 is benzyloxy,

R3 is hydrogen and

R4 is 1-4C-alkoxy,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

6. Compounds of formula 1 according to claim 3 in which

R1 is phenyl substituted by R2, R3 and R4,

wherein either

R2 is methylthio, methylsulfonyl or methylcarbonylamino,

R3 is hydrogen and

R4 is hydrogen,

or

R2 is benzyloxy and

R4 is methoxy,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

7. Compounds of formula 1 according to claim 3 in which

R1 is phenyl substituted by R2, R3 and R4,

wherein

R2 is aryl3,

R3 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino or mono- or di-1-4C-alkylaminocarbonyl and

R4 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

aryl2 is phenyl, furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl or triazinyl,

aryl3 is aryl2, aryl2 substituted by R5, R6 and R7, aryl4 or aryl4 substituted by R5, R6 and R7,

aryl4 is a condensed bicyclic ring system - of which at least one ring is aromatic - containing 8 to 10 carbon atoms, which optionally can be replaced by up to four heteroatoms selected from the group consisting of O, N and S,

R5 is halogen, hydroxyl, cyano, nitro, hydroxycarbonyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy completely or predominantly substituted by fluorine, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino, mono- or di-1-4C-alkylaminocarbonyl, mono-or di-1-4C-alkylaminosulfonyl or phenyl,

R6 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino or mono- or di-1-4C-alkylaminocarbonyl,

R7 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

8. Compounds of formula 1 according to claim 3 in which

R1 is phenyl substituted by R2, R3 and R4,

wherein

R2 is aryl 4, aryl2 or aryl2 substituted by R5, R6 and R7,

R3 is hydrogen, 1-4C-alkyl or 1-4C-alkoxy,

R4 is hydrogen, 1-4C-alkyl or 1-4C-alkoxy,

aryl2 is phenyl, furanyl, thiophenyl, pyrrolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl,

aryl4 is quinolinyl, benzo[1,3]dioxolyl, indolyl or naphthalenyl,

R5 is halogen, hydroxyl, cyano, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonylamino, di-1-4C-alkylamino or amino,

R6 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

R7 is hydrogen or 1-4C-alkoxy,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

9. Compounds of formula 1 according to claim 3 in which

R1 is phenyl substituted by R2, R3 and R4,

wherein either

R2 is aryl4, aryl2 or aryl2 substituted by R5, R6 and R7,

R3 is hydrogen,

R4 is hydrogen,

aryl2 is phenyl, furanyl, thiophenyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl or pyrimidinyl,

aryl4 is quinolinyl, benzo[1,3]dioxolyl, indolyl or naphthalenyl,

R5 is halogen, hydroxyl, cyano, 1-4C-alkyl, trifluoromethyl, methoxy, methoxycarbonyl, acetyl, methylcarbonylamino, dimethylamino or amino,

R6 is hydrogen, 1-4C-alkyl or 1-4C-alkoxy,

R7 is hydrogen or 1-4C-alkoxy,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

10. Compounds of formula 1 according to claim 3 in which

R1 is biphenyl-4-yl, 4-pyridin-2-ylphenyl, 4-pyridin-4-ylphenyl, 4-pyridin-3-ylphenyl, 4-(3,5-dimethyl-isoxazol-4-yl)phenyl, 4-thiophen-2-ylphenyl, 4-thiophen-3-ylphenyl, 4'-fluorobiphenyl-4-yl, 3'-fluorobiphenyl-4-yl, 4-benzo[1,3]dioxol-5-ylphenyl, 4-furan-3-ylphenyl, 4-pyridin-2-ylphenyl, 3'-carbonitril-biphenyl-4-yl, 4'-methoxy-biphenyl-4-yl, 3'-amino-biphenyl-4-yl, 4-(2,4-dimethoxy-pyrimidin-5-yl)phenyl, 3'-acetyl-biphenyl-4-yl, 4-quinolin-3-ylphenyl, 4'-trifluoromethyl-biphenyl-4-yl, 4-(2-methoxypyridin-3-yl)phenyl, 3',4'-dimethoxy-biphenyl-4-yl, 3'-methoxycarbonyl-biphenyl-4-yl, 3-furan-3-ylphenyl, 4'-methoxycarbonyl-biphenyl-4-yl, 4-(1H-indol-6-yl)phenyl, 3'-trifluoro-methyl-biphenyl-4-yl, 3-thiophen-3-ylphenyl, 3'-acetamide-biphenyl-4-yl, 3'-amino-biphenyl-3-yl, 3-furan-2-ylphenyl, 3'-methoxy-biphenyl-4-yl, 3-pyridin-4-ylphenyl, 3'-carbonitril-biphenyl-3-yl, 3-(3,5-dimethyl-isoxazol-4-yl)phenyl, 3-quinolin-3-ylphenyl, 3-pyridin-3-ylphenyl, 3'-fluorobiphenyl-3-yl, 3'-acetyl-biphenyl-3-yl, 3-(1H-indol-6-yl)phenyl, 3'-hydroxy-biphenyl-3-yl, 4-naphth-1-yl-phenyl, 3'-acetamide-biphenyl-3-yl, 4'-fluorobiphenyl-3-yl, 3-benzo[1,3]dioxol-5-ylphenyl, 4'-methoxycarbonyl-biphenyl-3-yl, 3-(6-methoxy-pyridin-3-yl)phenyl, 3'-methoxycarbonyl-biphenyl-3-yl, 3'-methoxy-biphenyl-3-yl, 4'-methoxy-biphenyl-3-yl, 4'-dimethylamino-biphenyl-4-yl, 2',3',4'-trimethoxy-biphenyl-4-yl, 3-(2,4-dimethoxy-pyrimidin-5-yl)phenyl, 4'-dimethylamino-biphenyl-3-yl, 3',4'-dimethoxy-biphenyl-3-yl, 4-(4-tert-butylthiazol-2-yl)phenyl, 3'-trifluoromethyl-biphenyl-3-yl, 2',3',4'-trimethoxy-biphenyl-3-yl, 3-naphth-1-ylphenyl,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

11. Compounds of formula 1 in which

R1 is 3-7C-cycloalkoxy substituted by R2, R3 and R4,

wherein either

R2 is hydroxyl, cyano, hydroxycarbonyl, trifluoromethyl, 1-4C-alkoxy completely or predominantly substituted by fluorine, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkyl-carbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylaminocarbon-yl, mono-or di-1-4C-alkylaminosulfonyl, phenoxy, benzyloxy or aryl3,

R3 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alk-oxycarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino or mono- or di-1-4C-alkylaminocarbonyl,

R4 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

or

R2 is halogen, hydroxyl, cyano, nitro, hydroxycarbonyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy completely or predominantly substituted by fluorine, 1-4C-alkylthio, 1-4C-alkylsul-fonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonylamino, amino, aminocar-

bonyl, mono- or di-1-4C-alkylamino, mono- or di-1-4C-alkylaminocarbonyl, mono-or di-1-4C-alkylaminosulfonyl, phenoxy, benzyloxy or aryl3,

R3 is 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl or mono- or di-1-4C-alkylaminocarbonyl,

R4 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

aryl2 is phenyl, furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl or triazinyl,

aryl3 is aryl2, aryl2 substituted by R5, R6 and R7, aryl4 or aryl4 substituted by R5, R6 and R7,

aryl4 is a condensed bicyclic ring system - of which at least one ring is aromatic - containing 8 to 10 carbon atoms, which optionally can be replaced by up to four heteroatoms selected from the group consisting of O, N and S,

R5 is halogen, hydroxyl, cyano, nitro, hydroxycarbonyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy completely or predominantly substituted by fluorine, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino, mono- or di-1-4C-alkylaminocarbonyl, mono-or di-1-4C-alkylaminosulfonyl or phenyl,

R6 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino or mono- or di-1-4C-alkylaminocarbonyl,

R7 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

12. Compounds of formula 1 in which

R1 represents a furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl or triazinyl group which is substituted by R2, R3 and R4,

wherein either

R2 is hydroxyl, cyano, hydroxycarbonyl, trifluoromethyl, 1-4C-alkoxy completely or predominantly substituted by fluorine, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylaminocarbonyl, mono-or di-1-4C-alkylaminosulfonyl, phenoxy, benzyloxy or aryl3,

R3 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino or mono- or di-1-4C-alkylaminocarbonyl,

R4 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

or

R2 is halogen, hydroxyl, cyano, nitro, hydroxycarbonyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy completely or predominantly substituted by fluorine, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbon-

yl, mono- or di-1-4C-alkylamino, mono- or di-1-4C-alkylaminocarbonyl, mono-or di-1-4C-alkylaminosulfonyl, phenoxy, benzyloxy or aryl3,

R3 is 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl or mono- or di-1-4C-alkylaminocarbonyl,

R4 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

aryl2 is phenyl, furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl or triazinyl,

aryl3 is aryl2, aryl2 substituted by R5, R6 and R7, aryl4 or aryl4 substituted by R5, R6 and R7,

aryl4 is a condensed bicyclic ring system - of which at least one ring is aromatic - containing 8 to 10 carbon atoms, which optionally can be replaced by up to four heteroatoms selected from the group consisting of O, N and S,

R5 is halogen, hydroxyl, cyano, nitro, hydroxycarbonyl, 1-4C-alkyl, trifluoromethyl, 1-4C-alkoxy, 1-4C-alkoxy completely or predominantly substituted by fluorine, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino, mono- or di-1-4C-alkylaminocarbonyl, mono-or di-1-4C-alkylaminosulfonyl or phenyl,

R6 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy, 1-4C-alkylthio, 1-4C-alkylsulfonyl, 1-4C-alkoxycarbonyl, 1-4C-alkylcarbonylamino, amino, aminocarbonyl, mono- or di-1-4C-alkylamino or mono- or di-1-4C-alkylaminocarbonyl,

R7 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

13. A compound of formula 1 selected from

2-(Quinolin-2-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,

2-(3,4-Dimethoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,

2-Cyclohexyl-4,5-dihydro-imidazo[4,5,1-ij]quinolin-6-one,

2-(4-Methoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,

2-(Thiophen-2-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,

2-(Pyridin-2-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,

2-(3-Hydroxy-4-methoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,

2-(3-Fluoro-4-methoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,

2-(3-Fluoro-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,

2-(1-Methyl-1*H*-pyrrol-2-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,

2-(3-Hydroxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,

2-(3-Methyl-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,

2-(2-Fluoro-4-methoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,

2-(3-Methoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,

2-(1*H*-Indol-5-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,

2-(3-Cyano-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,

2-(1*H*-Imidazol-4-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,

2-(Pyridin-3-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(Thiophen-3-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(3-Phenoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(3-Methoxycarbonyl-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(3-Trifluoromethoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(Furan-3-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one and
2-(3-Bromphenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
and the salts, the N-oxides and the salts of the N-oxides of these compounds.

14. A compound according to claim 13 for use in the treatment of diseases.

15. Use of a compound according to claim 13 for the production of pharmaceutical compositions for treating cancer, inflammation, ischemia/reperfusion injury during organ transplantation surgery, cerebral stroke, myocardial infarct and diabetes mellitus.

16. A compound selected from
2-(Naphthalen-2-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(4-Trifluoromethyl-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(4-Trifluoromethoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-Phenyl-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(3-Chloro-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(4-Bromphenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
and the salts, the N-oxides and the salts of the N-oxides of these compounds for use in the treatment of diseases.

17. Use of a compound selected from
2-(Naphthalen-2-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(4-Trifluoromethyl-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(4-Trifluoromethoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-Phenyl-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(3-Chloro-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(4-Bromphenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
and the salts, the N-oxides and the salts of the N-oxides of these compounds for the production of pharmaceutical compositions for treating cancer, inflammation, ischemia/reperfusion injury during organ transplantation surgery, cerebral stroke, myocardial infarct and diabetes mellitus.

18. A compound of formula 1 as claimed in one of the claims 3, 11 or 12 for use in the treatment of illnesses.

19. A pharmaceutical composition comprising at least one compound of formula 1 as claimed in one of the claims 3, 11 or 12 together with customary pharmaceutical excipients and/or vehicles.

20. A pharmaceutical composition comprising at least one compound of formula 1 as claimed in one of the claims 1, 13 or 16 together with customary pharmaceutical excipients and/or vehicles.

21. The use of compounds of formula 1 as claimed in one of the claims 3, 11 or 12 for the production of pharmaceutical compositions for treating cancer, inflammation, ischemia/reperfusion injury during organ transplantation surgery, cerebral stroke, myocardial infarct and diabetes mellitus.

22. Use of compounds of formula 1 as claimed in claim 1, 13 or 16 in the treatment of cancer, inflammation, ischemia/reperfusion injury during organ transplantation surgery, cerebral stroke, myocardial infarct and diabetes mellitus.

23. Use of compounds of formula 1 as claimed in claim 3, 11 or 12 in the treatment of cancer, inflammation, ischemia/reperfusion injury during organ transplantation surgery, cerebral stroke, myocardial infarct and diabetes mellitus.

24. Compounds of formula 1 acoording to claim 3 in which
R1 is phenyl substituted by R2, R3 and R4,
wherein either
R2 is 1-4C-alkylsulfonyl or 1-4C-alkylcarbonylamino,
R3 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy and
R4 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,
or
R2 is benzyloxy,
R3 is hydrogen and
R4 is 1-4C-alkoxy,
and the salts, the N-oxides and the salts of the N-oxides of these compounds.

25. Compounds of formula 1 according to claim 3 in which
R1 is phenyl substituted by R2, R3 and R4,
wherein either
R2 is methylsulfonyl or methylcarbonylamino,
R3 is hydrogen and
R4 is hydrogen,
or

R2 is benzyloxy,

R3 is hydrogen and

R4 is methoxy,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

26. Compounds of formula 1 according to claim 3 in which

R1 is biphenyl-4-yl, 4-(3,5-dimethyl-isoxazol-4-yl)phenyl, 4-thiophen-2-ylphenyl, 4-thiophen-3-yl-phenyl, 4'-fluorobiphenyl-4-yl, 3'-fluorobiphenyl-4-yl, 4-benzo[1,3]dioxol-5-ylphenyl, 4-furan-3-ylphenyl, 3'-carbonitril-biphenyl-4-yl, 4'-methoxy-biphenyl-4-yl, 3'-amino-biphenyl-4-yl, 4-(2,4-dimethoxy-pyrimidin-5-yl)phenyl, 3'-acetyl-biphenyl-4-yl, 4-quinolin-3-ylphenyl, 4'-trifluoromethyl-biphenyl-4-yl, 4-(2-methoxypyridin-3-yl)phenyl, 3',4'-dimethoxy-biphenyl-4-yl, 3'-methoxycarbonyl-biphenyl-4-yl, 3-furan-3-ylphenyl, 4'-methoxycarbonyl-biphenyl-4-yl, 4-(1H-indol-6-yl)phenyl, 3'-trifluoromethyl-biphenyl-4-yl, 3-thiophen-3-ylphenyl, 3'-acetamide-biphenyl-4-yl, 3'-amino-biphenyl-3-yl, 3-furan-2-ylphenyl, 3'-methoxy-biphenyl-4-yl, 3-pyridin-4-ylphenyl, 3'-carbonitril-biphenyl-3-yl, 3-(3,5-dimethyl-isoxazol-4-yl)phenyl, 3-quinolin-3-ylphenyl, 3-pyridin-3-ylphenyl, 3'-fluorobiphenyl-3-yl, 3'-acetyl-biphenyl-3-yl, 3-(1H-indol-6-yl)phenyl, 3'-hydroxy-biphenyl-3-yl, 4-naphth-1-ylphenyl, 3'-acetamide-biphenyl-3-yl, 4'-fluorobiphenyl-3-yl, 3-benzo[1,3]dioxol-5-ylphenyl, 4'-methoxycarbonyl-biphenyl-3-yl, 3-(6-methoxy-pyridin-3-yl)phenyl, 3'-methoxycarbonyl-biphenyl-3-yl, 3'-methoxy-biphenyl-3-yl, 4'-methoxy-biphenyl-3-yl, 4'-dimethylamino-biphenyl-4-yl, 2',3',4'-trimethoxy-biphenyl-4-yl, 3-(2,4-dimethoxy-pyrimidin-5-yl)phenyl, 4'-dimethylamino-biphenyl-3-yl, 3',4'-dimethoxy-biphenyl-3-yl, 4-(4-tert-butylthiazol-2-yl)phenyl, 3'-trifluoromethyl-biphenyl-3-yl, 2',3',4'-trimethoxy-biphenyl-3-yl, 3-naphth-1-ylphenyl,

and the salts, the N-oxides and the salts of the N-oxides of these compounds.

27. A compound of formula 1 selected from

2-(Quinolin-2-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,

2-(3,4-Dimethoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,

2-(4-Methoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,

2-(3-Hydroxy-4-methoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,

2-(3-Fluoro-4-methoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,

2-(3-Fluoro-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,

2-(1-Methyl-1*H*-pyrrol-2-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,

2-(3-Hydroxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,

2-(3-Methyl-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,

2-(2-Fluoro-4-methoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,

2-(3-Methoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,

2-(1*H*-Indol-5-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,

2-(1*H*-Imidazol-4-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,

2-(Thiophen-3-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,

2-(3-Methoxycarbonyl-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,

2-(3-Trifluoromethoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(Furan-3-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one and
2-(3-Bromphenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
and the salts, the N-oxides and the salts of the N-oxides of these compounds.

28. A compound of formula 1 selected from
2-(Acetylamino-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(3-Benzyloxy-4-methoxy-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(4-Methansulfonyl-phenyl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(3′-Acetamide-biphenyl-4-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
2-(3′-Acetamide-biphenyl-3-yl)-4,5-dihydro-imidazo[4,5,1-*ij*]quinolin-6-one,
and the salts, the N-oxides and the salts of the N-oxides of these compounds.

29. A compound according to one of the claims 24, 25, 26, 27 or 28 for use in the treatment of diseases.

30. Use of a compound according to one of the claims 24, 25, 26, 27 or 28 for the production of pharmaceutical compositions for treating cancer, inflammation, ischemia/reperfusion injury during organ transplantation surgery, cerebral stroke, myocardial infarct and diabetes mellitus.

INTERNATIONAL SEARCH REPORT

Internat ›plication No
PCT/Er 02/13973

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/06 A61K31/47 A61P9/10 A61P29/00 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
4 March 2003	14/03/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Guspanova, J

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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